Metaanalysis and review of heart failure disease management randomized controlled clinical trials

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Background The medical community has turned to disease management (DM) to bridge the gap between proven therapies and clinical practice for patients with heart failure (HF). The aim of this study was to assess the effectiveness of DM programs in reducing hospitalization and mortality in patients with HF on the basis of the results of existing trials.

Methods We compared the published results from 19 randomized controlled clinical trials evaluating HF DM programs. A random effects model was used to combine the hazards ratio for all-cause hospitalization across the studies evaluating specific types of HF DM programs.

Results We identified 19 relevant studies, with 5752 enrolled patients, which assessed the benefits of HF DM programs. The overall effect was a significant decrease in all-cause hospitalization for patients with HF. There was significant heterogeneity in the results ($P < .0001$).

Conclusions The results of this analysis indicate that HF DM is an intervention that could significantly decrease hospitalization for patients with HF. However, due to differences in the types of strategies and the variety of health care settings in which they were evaluated, further studies of HF DM programs with multiple participating centers are required. (Am Heart J 2005;149:722-9.)

The number of patients with heart failure (HF) is expected to reach 10 million by the year 2037.[1] Along with considerable clinical impact, HF places a significant economic burden on the American health care system. Caring for patients with this disease costs a total of $24.3 billion annually.[2]

The Institute of Medicine identified a significant gap between proven therapies and clinical practice in HF patient care, which it describes as a "quality chasm."[3] Disease management (DM) is viewed as a means to increase the use of evidence-based therapies, improve patient education, and decrease resource usage. Since the publication of the landmark study by Rich et al,[4] a number of studies have shown the benefit for patients with HF of providing additional interactions with the providers. These studies allowed for a comparison of different strategies for similar outcomes.

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This research was sponsored in part by the Porter grant (Cooperative agreement, No. 18-C-91677/4-01) from the Duke University Health System, Durham, NC, and the Department of Health and Human Services, Centers for Medicare and Medicaid Services, Baltimore, Md.

Submitted January 8, 2004; accepted September 16, 2004.

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0002-8703/$ - see front matter

doi:10.1016/j.ahj.2004.09.023

Methods

We searched MEDLINE for human, randomized, controlled trial results, published between 1966 and June 2003, using the following Medical Subject Headings: case management (exp); comprehensive health care (exp); DM (exp); health service research (exp); home care services (exp); clinical protocols (exp); patient care planning (exp); outpatient clinics, hospital (exp); ambulatory care facilities (exp); patient care team (exp); nurse led clinics (mp); and special clinics (mp). Each heading was cross-referenced with HF, congestive (exp). The results were reviewed and all studies reporting the use of a randomized controlled design were included in this study.

We reviewed all articles for patient characteristics, intervention characteristics, and outcomes, and identified the number of patients screened and enrolled. Other cohort characteristics included age, sex, ischemic versus nonischemic cardiomyopathy, comorbidities (hypertension, diabetes mellitus, and chronic obstructive pulmonary disease), New York Heart Association class, and left ventricular ejection fraction. Intervention characteristics included length of intervention and intensity of clinic, telephone, and home follow up. Cost of implementing the program was also included. Outcomes included medication use, quality of life (QOL) measurements, hospitalizations, mortality, and cost. The original investigators were contacted to clarify published results.

To compare different DM interventions, we used a random effects model to combine the hazards ratios for all-cause hospitalization across the studies evaluating specific types of HF DM. Because most HF DM randomized controlled trials evaluated patients hospitalized for HF and their postdischarge care, and evidence shows that this population of patients with

Table I. Program components and cost

Author	Country	No. of sites	Duration of intervention (wk)	Clinic visits	Telephone calls	Home visits	Estimated nurse	Estimated MD	Estimated cost
Clinic follow up, cardiologist supervision									
Cline et al[9]	Sweden	1	52	4	Yes, no. NR	NR	10 min/call, 30 min/visit	NR	$208/pt charge, $39/visit
Doughty et al[10]	New Zealand	1	8	4	NR	NR	NR	3 visits	NR
Kasper et al[11]	Maryland, United States	2	26	8.5	9.5/pt	PRN		4 visits	$904/pt, Outpt pharmacy
McDonald et al[12]	Ireland	1	13	2 + PRN	12/pt		RN: 1.7 h Dietitian: 1 h	NR	NR
Capomolla et al[13]	Italy	1	52	Yes, no. NR	Yes, no. NR	NR	NR	NR	$1243 ± 868
Clinic follow up, primary care supervision									
Weinberger et al[14] and Oddone et al[15]	VA centers, United States	9	26	1	1 + PRN	NR	Calls 7.5/pt, 5.7 min/call	17.2 vs 14.1, $P < .001$	NR
Ekman et al[16]	Sweden	1	26	1 PRN, 23/79 with 0	4/pt, 51% US call	NR	NR	NR	NR
Home visits									
Rich et al[4]	Missouri, United States	1	13	None	Yes, no. NR	Yes, no. NR	7.2 h/pt	NR	$216/pt, $336/pt care giver
Stewart et al[17,18]	Australia	1	1	PRN	NR	1	NR	NR	$190/pt (Australian dollars)
Stewart et al[19]	Australia	1	1-2	38% after home visit	159 calls	1	Visit: 2 h	NR	$350/pt (Australian dollars)
Jaarsma et al[21]	Netherlands	1	1.5	None	1	1	NR	NR	NR
Hughes et al[22]	VA centers, United States	16	52 (ave 24)	0.85/pt	PRN	Yes, no. NR		24 h/mo	$282/pt/mo, $3000 for study
Harrison et al[23]	Canada	1	2	NR	1	PRN	NR	NR	NR
Blue et al[24]	Scotland	1	52	None	Yes, no. NR	Yes, no. NR	NR	NR	NR
Telephone follow up									
Riegel et al[25]	California, United States	2	26	PRN	14 calls/pt	NR	$26.51/h, 16 h, 130 pt/RN	5.63 vs 6.17, P = NS	$443, included 95 h of training
Krumholz et al[26]	Connecticut, United States	1	52	2	17	45% with home visit	$50/h RN/SW, 5 h/pt RN, 2 h/pt SW	NR	$530/pt
Laramee et al[27]	Vermont, United States	1	13	19	9, 5-45 min/call	NR	65-89 pt/RN, 6.7 h/pt	PRN	$228.52
Stable HF patient clinic follow up, cardiologist supervision									
Gattis et al[28]	North Carolina, United States	1	26	1 PRN	3	NR	NR	NR	NR
Ansari et al[29]	California, United States	1	26			NR			NR

NR, not reported; *NS*, not significant; *Outpt*, outpatient; *pt*, patient; *PRN*, as needed; *RN*, registered nurse; *SW*, social work; *US*, unscheduled.

HF is different in readmission risk, we focused our evaluation on this group of studies.[5] Specifically, an Empirical Bayes' estimator as described by Hedges and Olkin[6] was used in this metaanalysis. This particular estimator works well for as few as 2 studies, and if the studies are homogeneous, the estimates approach those of the fixed effects model. The calculations were carried out using Fast*Pro software (Academic Press, Inc, Orlando, Fla).[7]

Results for hospitalized elderly patients with HF were used to estimate control hospitalization rate.[8] The estimates of the hazard rate were based on the Weibull model, with estimated parameters set at $\lambda = 0.187$ and $\alpha = 0.618$. The value of λ was

Table II. Baseline characteristics of enrolled patients

Author	Number screened	Number randomized	Age (y)	% Female	% ICM	LVEF (%)	NYHA (II/III/IV%)	% on ACEi	% on BB
Clinic follow up, cardiologist supervision									
Cline et al[9]	NR	190	75.6	47	53	34%, 75% < 40	NR/62/NR, mean 2.6	22	10
Doughty et al[10]	NR	197	73	30	54	32 ± 13	0/24/76	89	NR
Kasper et al[11]	1252	200	63.5	40	49	87% < 45	35/59/NR	86	39
McDonald et al[12]	337	98	71	34	47	37 ± 13	NR	98	NR
Capomolla et al[13]	NR	234	56	16	41	29 ± 7	I-II: 153, III-IV: 81	97	40
Clinic follow up, PCP supervision									
Weinberger et al[14] and Oddone et al[15]	10129	504	65	1	NR	65% < 40	37/34/18, 11 Class I	60	12
Ekman et al[16]	1058	158	80	42	68	40, 40% > 40	NR, ave 3.2	37	30
Home visits									
Rich et al[4]	1306	282	79	63	56	42	NR, ave 2.4	59	12
Stewart et al[17,18]	107	97	75	52	67	38	51/45/4	81	NR
Stewart et al[19]	4055	200	75	38	78	37	45/44/11	71	28
Jaarsma et al[21]	644	186	73	42	52	34.4 ± 14	0/39/61	70	NR
Hughes et al[22]	2202	1966	70	4	NR	NR	NR	NR	NR
Harrison et al[23]	483	192	76	45	NR	NR	22/67/10	NR	NR
Blue et al[24]	801	165	75	42	54	NR	21/38/41	76	5
Telephone follow up									
Riegel et al[25]	1145	358	72	51	49	42.7 ± 18.2	3/37/60	54	17
Krumholz et al[26]	398	88	74	43	61	38 ± 17	NR	60	41
Laramee et al[27]	589	287	70.7	46	71	80% < 55	46/35/3	82*	63
Stable HF patient clinic follow up, cardiologist supervision									
Gattis et al[28]	1568	181	67	32	22	30	54/30/3	78	NR
Ansari et al[29]	857	169	70	3	NR	35% < 30	NR	81	34

ACEi, ACE inhibitor; *BB*, ß blocker; *ICM*, ischemic cardiomyopathy; *LVEF*, left ventricular ejection fraction; *NYHA*, New York Heart Association; *VA*, Veterans Affairs.
*ACEi and ARB reported together.

adjusted so that the model would give this estimated rate at 6 months. An estimate of the hospitalizations per year was obtained by integrating the hazard function from 0 to 12 months, using Mathematica (Wolfram Research, Inc, Champaign, Ill).

Results

An initial MEDLINE search resulted in 1344 citations, from which we identified 19 randomized controlled trials evaluating HF DM.[4,9-29] Although 2 studies by Naylor et al[30,31] included patients with HF, results were not reported separately for this subgroup. Therefore, those studies were not included as part of the analysis.

Postdischarge HF DM

All interventions included a predischarge component. Most studies included DM strategies after an HF admission. Four types of postdischarge intervention identified were (1) clinic follow up by a physician extender with cardiology supervision, (2) clinic follow up by a physician extender with primary care physician (PCP) supervision, (3) home nursing follow up, or (4) telephone follow up by a physician extender. Although many studies included more than 1 type of postdischarge care, the studies were categorized on the basis of the primary means for patient follow up.

The interventions present a wide variation in intensity including intervention duration, time requirements, and cost (Table I). Unfortunately, many manuscripts did not provide specific details regarding program components, personnel efforts, or cost. Of the 19 studies included in this metaanalysis, 9 were conducted in the United States and the others were conducted in Canada, Europe, and Australia. Only 4 studies enrolled patients at multiple sites.

Patients included in the study were similar in the reported characteristics (Table II). The ratio of screened to enrolled patients ranged from 1.1 to 20.3 screened patients for every enrolled patient. Of the 5752 patients enrolled in these studies, the majority was older than 70 years. There was good representation of female patients, except for studies based at Veterans Affairs medical centers. Although minority enrollment was not reported for studies performed in European countries, the representation was good in studies performed in the United States. The prevalence of diseases in the studies ranged from 19% to 52% for diabetes, 29% to 76% for hypertension, and 19% to 36% for chronic obstructive pulmonary disease. Although most patients had left ventricular function <40%, a number of studies enrolled patients with greater function, which is consistent with

Table III. Outcomes

Author	Follow up (m)	Readmissions/LOS (d) (Int vs Cont)	Mortality % (Int vs Cont)	Cost (Int vs Cont)
Clinic follow up, cardiologist supervision				
Cline et al[9]	12	AC per pt: 0.7 ± 1.1 vs 1.1 ± 1.8 AC LOS: 4.2 vs 8.2	30 vs 28	Inpt: $1628 vs $3594 Total: $2294 vs $3594
Doughty et al[10]	12	AC: 120 vs 154; CHF: 36 vs 65 LOS AC: 8.9 vs 7.6; CHF: 9.9 vs 8.6	19 vs 24	NR
Kasper et al[11]	6	AC: 77 vs 96; CHF: 43 vs 59 LOS 6.3 vs 4.8	7 vs 13	Pharmacy: $1353 vs $1405 Inpt: $11 315 vs $8789
McDonald et al[12]	3	CHF: 1 vs 11* Index LOS: 13.7 vs 14.6	3 vs 1	NR
Capomolla et al[13]	12	AC: 13 vs 78, $P < .00001$	3 vs 21‡	Drug: $741 vs $490‡ Inpt: $268 vs $1332‡
Clinic follow up, primary care supervision				
Weinberger et al[14] and Oddone et al[15]	6	% pt AC: 56 vs 44*; CHF: 29 vs 30 Hospital days 9.1 vs 7.3†	13.1 vs 8.6	NR
Ekman et al[16]	5	AC: 61 vs 57; days: 15 vs 11	27 vs 22	NR
Home visits				
Rich et al[4]	3	AC: 53 vs 94†; CHF: 24 vs 54† ALOS: 10.5 vs 9.2	9.2 vs 12.1	Inpt: $2178 vs $3236† Overall: C > I $153/pt/mo
Stewart et al[17,18]	6/18	AC unplanned: 36 vs 63†/64 vs 125† ER visit: 48 vs 87†/2.5 vs 4.5*	6:6 vs 12 18:11 vs 20†	Inpt/pt: $3200 vs $5400 Outpt/pt: $620 vs $680
Stewart et al[19]	6	AC: 68 vs 118†; HF: 34 vs 58 ALOS: 6.8 vs 9.9	18 vs 28	Hospital cost $900 vs $2200
Stewart and Horowitz[20]	50	Adm/pt/mo: 0.17 vs 0.29† ALOS: 8.2 vs 8.8, P = NS	RR 0.72 (0.54-0.97)†	Hospital cost/pt/mo $325 vs $660*
Jaarsma et al[21]	9	% pt AC: 37 vs 50, CV: 29 vs 39 AC day/pt: 9 vs 9, P = NS	26 vs 17	NR
Hughes et al[22]	12	AC: 3.6 vs 2.0	NR	$31 401 vs $28 008*
Harrison et al[23]	3	AC% pt: 23% vs 31%, P = NS ER% pt: 29% vs 46%, P = .03	9 vs 11	NR
Blue et al[24]	12	AC: 86 vs 114†, CHF: 19 vs 45‡ days/pt AC: 10 vs 17; CHF: 3.4 vs 7.5*	30 vs 31	NR
Telephone follow up				
Riegel et al[25]	6	AC/pt: 0.062 vs 0.87, HF/pt: 0.21 vs 0.41† Day/pt AC: 3.5 vs 4.8, HF: 1.1 vs 2.1†	12.3 vs 14	Inpt HF cost: $1192 vs $2186†
Krumholz et al[26]	12	AC: 49 vs 80, HF: 22 vs 42 Day/pt AC: 10 vs 15, HF: 4.1 vs 7.6	9 vs 13, P = .33	Inpt: $14 420 vs $21 935† Overall $6985 less
Laramee et al[27]	3	AC: 70 vs 61 AC day/pt: 6.9 vs 9.5	13 vs 15	Outpt: $1552 vs $1307 Inpt: $5253 vs $5163
Stable HF patient clinic follow up, cardiologist supervision				
Gattis et al[28]	6	HF: 1 vs 11*	3 vs 5	NR
Ansari et al[29]	12	CHF: 12% vs 10% AC: 44% vs 49%	5 vs 14	NR

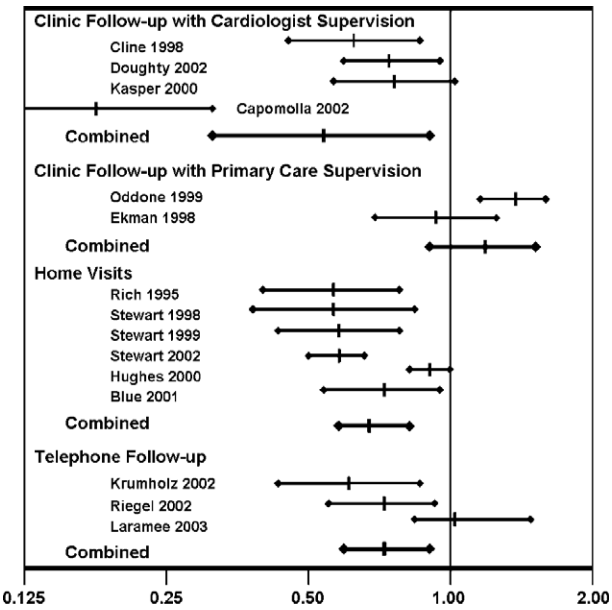
AC, all-cause; *Adm*, admissions; *ALOS*, average length of stay; *CHF*, congestive HF; *Cont*, control arm; *CV*, cardiovascular; *Inpt*, inpatient; *Int*, intervention arm; *LOS*, length of stay.
*$P < .01$.
†$P < .05$.
‡$P < .001$.

the older population enrolled in the studies. Of the 19 studies, 12 reported angiotensin-converting enzyme (ACE) inhibitor use of at least 60%; β blocker use was limited.

Heart failure DM had mixed impact on medication use, QOL, and mortality (Table III). The limited reporting of medication use (6 of 17 postdischarge studies), particularly in the studies evaluating home visit DM, does not allow any definitive statement regarding how DM might change medication use. In general, there was a modest increase in ACE inhibitor use. There was more consistent improvement in QOL, both in disease-specific and general measurements. There was no difference in mortality except in the studies by Stewart et al[18,20] and Capomolla et al.[13]

Metaanalysis of hospitalization revealed that DM interventions using clinic follow up by a cardiologist, home visit, or telephone follow up significantly decreased all-cause hospitalization for patients with HF (Figure 1). The McDonald et al[12] study was not included in the metaanalysis because they did not report all-cause mortality. As seen in Figure 1, there was a significant

Figure 1



Relative risk point estimate and 95% CI for all-cause hospitalization for postdischarge HF DM randomized control trial.

heterogeneity in the results ($P < .0001$). Disease management involving clinic follow up with PCP supervision had a relative risk point estimate of >1 (1.17, 95% confidence interval [CI] 0.90-1.51) suggesting that this type of DM did not provide a decrease in all-cause hospitalization. Excluding the studies with PCP supervision, the overall point estimate for HF DM showed a significant decrease in HF hospitalization of 35.1%.

Decreases in HF hospitalizations were the primary cause of a decrease in all-cause hospitalization (Table III). Consistent with the decrease in all-cause and HF hospitalization, the number of hospital days per patient and inpatient cost declined with HF DM, with the exception of clinic follow up DM supervised by a PCP. Only 1 study evaluated the impact of DM on patient pharmacy cost and found very little change despite the increased use of ACE inhibitors and β blockers.[11]

The analysis predicted patients receiving usual care would have, on average, 1.08 hospitalizations per year. Given the relative risk estimate from the metaanalysis, the estimated reduction is 50.1% for clinic follow up with cardiology supervision, 37.4% for home visit DM, and 34.7% for telephone follow up. The greater reduction by clinic follow up with cardiology supervision was primarily due to the study by Capomolla. Excluding this study, the estimated reduction for clinic follow up with cardiologist is 27.3%. The model found that clinic follow up with PCP supervision would increase the chance of all-cause hospitalization by 18.1%.

Chronic outpatient HF DM

Not included in the metaanalysis were 2 studies that enrolled stable patients with HF in the outpatient setting.[28,29] Both were clinic-based studies involving a nonphysician health care provider (PharmD or nurse practitioner) as the primary person interfacing with patients. The primary focus of both studies was improved medication use: ACE inhibitors in the study by Gattis et al[28] and β blockers in the study by Ansari et al.[29] Although the primary intervention was clinic based, there were scheduled telephone calls to patients for follow up. Medication use improved in both, but only the study by Gattis et al showed a significant reduction in hospitalizations.

Discussions

For patients with HF being discharged from the hospital, this metaanalysis demonstrates that most DM interventions significantly decrease rehospitalization. There was a trend for better outcomes in patients with clinic follow up with cardiology supervision, but this finding was heavily influenced by 1 positive study.[13]

In 2 studies of clinic follow up with PCP supervision, no additional benefit was demonstrated. One possible explanation for this finding is the significant difference in the use of HF medications and diagnostic testing between cardiologists and noncardiologists.[32-34] Although clinical studies of HF medications found a decrease in hospitalizations as well as improved survival, differences in outcomes for HF patients cared for by a cardiologist versus noncardiologist have been reported primarily for survival, not hospitalization.[35-38] We caution making any final conclusion regarding the supervision by PCPs because only 2 studies were used in this category of HF DM. For some studies with home and telephone follow up that had improved outcomes, PCPs were the primary patient contact.

The underlying reason for the improvement in hospitalization is difficult to identify on the basis of the current studies. It is unlikely due to improved medication use. Although HF medications such as ACE inhibitors and β blockers decrease hospitalizations in large clinical trials, 6 months is required before improvement is seen (when hospitalization curves separate).[36-38] Most of the studies in this analysis had follow-up times of 6 months or less. In addition, many studies reported improved outcomes with no significant change in medication use.[10,11,29] Although constrained by the limited reporting of medication use, the lack of change in ACE inhibitor and β-blocker use is particularly surprising because these studies primarily took place after publication of large randomized clinical trials evaluating these drugs.[36-38]

One possible cause for the decease in hospitalizations is an increase in access to health care providers. This

increased access allows for a higher level of surveillance and earlier detection of patients who are becoming unstable or experiencing weight gain before a hospital admission. Unfortunately, it is difficult to detect a trend in improved outcome with the increased intensity of the intervention. Studies by Stewart et al seem to contradict any relationship between intensity and outcome. With only 1 home visit after discharge and a subsequent clinic contact, if necessary, the investigators found a significant decrease not only in hospitalizations and emergency room (ER) visits but also in mortality.

The economic impact of HF DM is difficult to assess on the basis of the randomized controlled trials used in this analysis. Although most of the studies reported a cost for providing the intervention, it only reflected estimates of direct personnel expenses. Indirect expenses such as increased physician time outside the intervention, patient materials, or other start-up costs were not included. Most cost savings reported as outcomes were for inpatient or hospital costs. They did not take into account the loss of revenue created by decreased hospitalizations and the impact that this might have on a health care system. Only the study by Kasper et al[11] reported patient pharmacy costs. Due to the lack of improvement in medication use provided by the intervention, there were no significant differences between the intervention arm and the usual care arm ($1353 vs $1405, P = NS).

Although this metaanalysis shows a similar overall benefit of HF DM on all-cause hospitalization as a previous metaanalysis, the evaluation of types of DM programs results in a different conclusion. The study by McAlister et al[39] concluded that a multidisciplinary team approach (RR 0.77, 95% CI 0.68-0.86) was superior to telephone contact and enhanced communication with PCPs (RR 1.15, 95% CI 0.96-1.37). Although the conclusion of the current metaanalysis supports the lack of benefit of PCP supervision for an HF DM program, this analysis supports the use of telephone follow up with cardiologist supervision. The discrepancy in results may be due to fewer studies (11) being included in the previous metaanalysis. The larger number of studies (19) in the current metaanalysis allowed us to categorize interventions on the basis of a standard classification scheme.[40]

Limitations: Implications for Medicare reimbursement of DM programs

The positive outcomes of the studies used in this analysis will be difficult for many providers and health care organizations to achieve. Lack of details about the intervention design creates a significant amount of uncertainty about the resources required to replicate the results (Table I). None of the studies considered societal costs such as patient or family time spent participating in the intervention. The economic benefit that a provider, health care organization, payer, or society will achieve with DM remains uncertain.

The variation in the geographic location of these studies, with significant differences in health care systems and reimbursement, increases the risk that implementing a strategy proven successful in one location will provide similar cost reductions in another. The importance of geography on outcomes has been identified in previous randomized controlled clinical trials.[41,42] In the United States, geography was an independent predictor of ACE inhibitor use from 1989 through 1994.[34] This regional variation may have played a role in the positive findings by Stewart et al, because the site of the study (Adelaide, South Australia) is a rural area in which access to health care may be significantly different than in other areas of Australia or in other countries.

Most of these studies were single-center evaluations. Only having success within small single-center studies raises concerns about bias. Although investigators and patients cannot be blinded regarding which arm of a study an enrollee is participating in, there is no independent review or adjudication of end points, which leaves the findings of studies open to criticism. The 4 studies enrolling patients at >1 site did not detect a significant change in all-cause hospitalization, and only 1 study reported a significant decrease in HF hospitalization. The ability of investigators to work with local providers has been identified as an important factor by Laramee et al.[27] In this study, telephone monitoring had a significant impact for patients cared for by local cardiologists. The investigators suggested that it was the ability of case managers to communicate easily with providers and the providers' trust in familiar case managers that created this benefit.

Conclusion

On the basis of the current metaanalysis, HF DM is an intervention that could significantly decrease hospitalizations for patients with HF. Unfortunately, due to significant limitations in the current studies, our understanding of the potential underlying mechanism for improving outcomes remains limited. It is difficult to generalize the vastly different interventions performed in a number of health care settings, as is evidenced by the current lack of success seen in the multicenter studies included in this analysis. Further evaluation of HF DM with multiple participating centers is required before payers should feel comfortable that results from individual studies and this metaanalysis will be achieved when covering the costs of HF DM.

We thank Deana Betterton-Lewis for manuscript preparation and editorial assistance.

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